Food Additives and Contaminants Committee

The terms of reference of the Food Additives and Contaminants Committee were:

'To advise the Minister of Agriculture, Fisheries and Food, the Secretary of State for Social Services, the Secretary of State for Wales, the Secretary of State for Scotland and, as respects Northern Ireland, the Head of the Department of Health and Social Services, on matters referred to it by Ministers in relation to food contaminants, additives and similar substances which are, or may be, present in food or used in its preparation, with particular reference to the exercise of powers conferred on Ministers by sections 4, 5 and 7 of the Food and Drugs Act 1955 and the corresponding provisions in enactments relating to Scotland and Northern Ireland.'

In November 1983 the Food Additives and Contaminants Committee was merged with the Food Standards Committee to form the new Food Advisory Committee.

The members of the Food Additives and Contaminants Committee at the time of completion of this Report were:

B C L Weedon, Esq, CBE, DSc, PhD, ARCS, DIC, D Tech, C Chem, FRSC, FRS *(Chairman)*
P J Brignell, Esq, BSc, PhD, C Chem, MRSC
J W Colquhoun, Esq, BSc, FIFST, FBIM
W Elstow, Esq, BSc, PhD, M Chem A, C Chem, FRSC, FIFST
T T Gorsuch, Esq, BSc, PhD, FIFST
A J Harrison, Esq, M Chem A, C Chem, FRSC, FIFST, FRSH
Professor June K Lloyd, MB, MD, ChB, FRCP, DPH
Professor I MacDonald, MD, DSc, FIBiol
D S McLaren, Esq, MB, ChB, MD, DTM&H, PhD, FRCP (Edin)
Professor J W G Porter *(deceased)*, MA, PhD, FIBiol
G M Telling, Esq, MSc, M Chem A, C Chem, FRSC
Professor P Turner, MD, BSc, FRCP, Hon MPS, Hon FIBiol
Mrs Lesley Yeomans, BSc, PhD

The following also served on the Committee during the preparation of this Report:

W R Bannatyne, Esq, BSc, PhD, FIFST
R B Beedham, Esq, BSc, C Chem, MRSC, FIFST

Mrs Janet R Cockcroft, OBE, MB, ChB
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Professor J R Norris, BSc, PhD, FIBiol
Professor D V W Parke, DSc, PhD, C Chem, FRSC, FIBiol, FRC Path
W Price-Davies, Esq, BSc, C Chem, MRSC
R Sawyer, Esq, BSc, C Chem, FRSC
Professor Patricia P Scott, MBE, BSc, PhD, FIBiol
D J Ward, Esq *(deceased)*, C Chem, FRSC, FIFST
Professor E F Williams, OBE, MA, FRSC, FIPHH, MRSH, FIFST

Joint Secretaries

M J Griffiths, Esq
W H B Denner, Esq, BSc, PhD

Acknowledgements

J C Sherlock, Esq, BSc, PhD, MICorrT was responsible for the collection and presentation of a considerable amount of the scientific and technical information required for this Review.

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REPORT ON THE REVIEW OF THE ARSENIC IN FOOD REGULATIONS

Introduction

1. We were asked to review the Arsenic in Food Regulations 1959(a), as amended(b), and to consider whether, and if so to what extent, amendments to the Regulations were necessary in the light of present conditions. As part of the review we were also asked to take account of the data obtained by the Working Party on the Monitoring of Foodstuffs for Heavy Metals during their survey of arsenic in food(c). We have done this and we have also taken account of representations received as a result of the announcement of our Review in August 1975. A list of those organisations which made representations or supplied information is given at Appendix I.

2. We asked the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) to consider the medical aspects of arsenic in food. We accept the recommendations in their Report which is attached as Appendix II to this Report.

The Monitoring Programme

Report of the Working Party on the Monitoring of Foodstuffs for Heavy Metals

3. The Working Party on the Monitoring of Foodstuffs for Heavy Metals was set up in 1971 to determine amongst other things the levels at which traces of heavy metals occur in food in the United Kingdom. Its reports, which are submitted to this Committee and the COT, are published through its parent body, the Steering Group on Food Surveillance, an interdepartmental expert committee whose function inter alia is to keep specific food contamination problems under review, assess the needs for analytical surveys of food, and where appropriate make arrangements for these surveys to be carried out. The Working Party dealt with arsenic in food in its report published as the Eighth Report of the Steering Group. The Report presented information on the intake of arsenic from total diet studies and the results of a survey of arsenic in a wide variety of individual foods. These foods

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(a) SI 1959 No. 831 (For convenience, reference is made throughout this Report to the legislation applying in England and Wales. In each case, separate but similar legislation exists for Scotland and Northern Ireland.

(b) SI 1960 No. 2261, SI 1962 No. 1287, SI 1963 No. 1435, SI 1972 No. 1391, SI 1973 No. 1052, SI 1973 No. 1340, SI 1975 No. 1486 and SI 1982 No. 1727

(c) The Eighth Report of the Steering Group on Food Surveillance, 'Survey of Arsenic in Food' (HMSO 1982) included fish and shellfish (which have a known propensity to accumulate arsenic) and foods from areas likely to be affected by local sources of contamination. Very few of the samples exceeded the maximum arsenic concentrations prescribed in the Arsenic in Food Regulations 1959, as amended, and virtually all the foods analysed were substantially below those concentrations. The Working Party's Report indicated that the daily intake of arsenic for the average person was extremely low, and this main conclusion has had a particular bearing on our Review; it did however also draw attention to the particular circumstances affecting the arsenic content of fish and shellfish and of pig kidney and pig liver, and we refer to these items again at paragraphs 16 to 18 and 21 to 22 respectively.

Results

4. The results of the Working Party survey indicated that the intake of arsenic from the 1.46 kg of food consumed daily by the average person in the United Kingdom is about 90 µg per day. The FAO/WHO suggested a maximum acceptable daily body load for arsenic of 3.5 mg (3500 µg) for a 70 kg adult. This figure is for the total arsenic intake from all chemical forms. The COT has estimated that a daily ingestion of about 1.5 mg (1500 µg) of inorganic arsenic is likely to result in signs of chronic arsenic toxicity. Most of the arsenic in the average UK diet originates from fish and is thus present in the organic form, which is probably less toxic than the inorganic form. Therefore, not only are total dietary arsenic intakes in the United Kingdom low, but inorganic arsenic is a minor component of this intake.

Reconsideration of the Statutory Limits

Present general limit

5. The present Regulations impose a general limit of one part per million arsenic in food, but for certain foods there are specified limits which are either higher or lower than the general limit. Foods (including additives) for which maximum permitted arsenic levels are prescribed in other Regulations made under the Food and Drugs Act 1955(a) are exempt from the provisions of the Arsenic in Food Regulations. There are also specific exemptions from the general limit in the case of fish and edible seaweed if arsenic is naturally present, and of hops or hop concentrates intended for commercial brewing: we discuss these further at paragraphs 16 to 18 and 12.

(a) 4 Eliz. 2. Ch. 16

6. The present general limit of one part per million was first proposed in 1949 by the Metallic Contamination Sub-Committee of the Food Standards Committee, although before then, in 1903, a Royal Commission had recommended similar limits which had served as standards in good commercial practice and were accepted as recognised limits in the courts. The Food Standards Committee in their 1955 Report(a) confirmed the 1949 proposed level. These recommended limits, and the later statutory controls, were all introduced to effect control over arsenical contamination arising during the industrial preparation and manufacture of food and the then widespread use of arsenical pesticides in fruit and vegetables. The information made available to us during the Review showed that improvements in these areas had been achieved by the food manufacturing and related industries; and this is reflected in our recommendations.

Need for continued statutory control on arsenic content of food

7. In their Report (Appendix II to this Report) the COT considered that the reported arsenic levels in the diet indicated no cause for concern and that there was no toxicological basis for a reduction in the levels permitted in foods and beverages. The evidence we have seen also indicates that the level of arsenic contamination has decreased over the last two decades. This has been due in part to changed manufacturing processes and also to a decrease in the amount of lead arsenate sprayed on agricultural crops.

8. In the light of these findings we have considered whether or not there is a need for continued specific control on the arsenic content of food and whether, for example, this particular contaminant could be dealt with adequately by the general provisions of the Food and Drugs Act.

9. In our consideration we have recognised that the existence of detailed regulations imposes a cost on both industry and the enforcement authorities; and that various other contaminants and medical additives are not controlled by regulations based on levels detected in the final food. On the other hand there are arguments for maintaining an existing control. For example, there is reason to believe that the existing Regulations have contributed to the present very satisfactory position with respect to arsenic in food; and retention of the Regulations would help to ensure that this situation continues. Retention of statutory levels in Regulations would continue to provide

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(a) Food Standards Committee: Report on Arsenic, FSC/MC/REP 13 (HMSO 1955) enforcement authorities with a basis for monitoring levels of arsenic in food, and would be more likely to encourage continued surveillance of the position by those authorities and by industry.

10. On balance, we consider that the Regulations should be maintained. However, we *recommend* that when a suitable opportunity arises the Regulations should be amended and, in particular, considerably simplified, to take account of the improvements and changes in agricultural and food manufacturing practice over the past 25 years. We consider below how this should be done.

Expression of future limits

11. The present limits are expressed in terms of parts per million (ppm) by weight. To conform with modern usage we consider that limits in future Regulations should be expressed in milligrams per kilogram (mg/kg), as is now the case with the Lead in Food Regulations 1979[a] following our recommendation to similar effect in our Review of the Lead in Food Regulations 1961[b]. We *recommend* accordingly.

Proposed general limit

12. In the light of the results of the analyses of food which were made available to us, we are satisfied that the vast majority of foods could now comply with the existing general limit of 1 ppm, which should be attainable under conditions of good manufacturing practice. In view of the conclusions of the COT, we also consider that the existing limit would continue to provide an acceptable level of protection for the consumer and that there is therefore no need for it to be further reduced. There is no advantage in setting unnecessarily low limits which could result in the rejection of food to no good purpose. We accordingly *recommend* that the general limit should remain at 1.0 mg/kg; though in view of the developments to which we have already referred, we do not consider there to be any longer a need for a specific exemption from this limit for hops and hop concentrates intended for commercial brewing.

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[a] SI 1979 No. 1254

[b] Food Additives and Contaminants Committee: Review of the Lead in Food Regulations 1961, FAC/REP/21 (HMSO 1975)

Definition of 'substantial quantity'

13. The present Arsenic in Food Regulations make special provision to permit the sale of certain foods which may not comply with the general limit of 1 ppm. This permission applies to foods containing a 'substantial quantity' (not less than 25%) of an ingredient subject to a specified arsenic limit greater than the general limit. We are satisfied that there remains a need for such provision, but we suggest a change to bring it into line with the equivalent provision introduced into the Lead in Food Regulations 1979 as a result of our Review of the earlier Regulations. We accordingly propose that any specified food which individually accounts for at least 10% of the total weight of the food should be allowed to increase the arsenic level permitted in the compound food. The amount of arsenic permitted would, as now, be calculated from the amount of each food present – and each ingredient would have to comply with the appropriate individual limit if it was sold separately.

14. During our Review of the earlier Lead in Food Regulations it also emerged that certain highly specialised additive premixes, which are formulated and sold only for use by food manufacturers and processors, could give rise to problems in this area. Such premixes could contain individual ingredients with levels of lead in excess of the general limit of 1 ppm to which the premix as a whole would normally have been subject. However, the form of defence outlined at paragraph 13 of this Report would not have applied to such products because some of the ingredients contributed less than 10% by weight of the mixture. We therefore consider that any new arsenic Regulations should include provision for a further defence in respect of the arsenic content of such additive premixes equivalent to that presently afforded in the Lead in Food Regulations 1979. This should apply in the case of an additive premix consisting of a mixture of substances for use as an ingredient in the preparation of food providing it is in a container clearly identifying its purpose and non-retail nature; and it should provide a defence against contravention of the limits specified in the Regulations if the ingredients of the additive premix would not have contravened the Regulations if sold separately. As in the case of the Lead in Food Regulations we propose that the onus of proof should rest on the manufacturer in the event of any dispute. We *recommend* accordingly.

Foods with Existing Specified Limits

General

15. The existing Regulations include a Schedule of Foods which may contain amounts of arsenic differing from the general limit. These special limits are based on the recommendations of the Food Standards Committee in their Report on Arsenic of 1955 and reflect the manufacturing practices, analytical methods and other factors existing at that time. In particular, contamination was likely to arise in the past when foods were dried using fuel containing arsenic; when they were treated with sulphur or sulphur compounds themselves contaminated with arsenic; and when sprayed with arsenic compounds. Contamination from these sources has declined over the years, due in part to changes in manufacturing processes and by a considerable decrease in the amount of lead arsenate sprayed on agricultural crops. This trend has been evident from the considerable amount of analytical data relating to individual foods which has been available to us. In the light of these changes we have concluded that exceptions to the general limit are now only justified in the limited number of cases considered below.

Fish and edible seaweed and products containing fish and edible seaweed

16. Regulation 3 of the Arsenic in Food Regulations, which imposes a general limit of 1 ppm, also provides for fish and edible seaweed or any product containing fish or edible seaweed to exceed the limit if the arsenic is naturally present in the fish or edible seaweed, or is present in the product containing them, by reason of its fish or edible seaweed content. This provision took account of the presence in fish, processed fish, crustacea, shellfish, seaweed, etc, of ‘natural’ organically bound arsenic and coincided with the general philosophy of the Regulations which was to control ‘adventitious’ arsenic.

17. We are aware that in practice this provision has caused some problems for the authorities charged with enforcing the Regulations, since fish often contains more arsenic than other foods but in a different chemical form to inorganic arsenic. However, we have noted and agreed with the view of the COT (Appendix II) that there is no evidence at present that intake of arsenic naturally present in fish presents a hazard to human health: indeed, it is probably less toxic than inorganic arsenic compounds. Under the circumstances therefore, we do not consider there to be any need to lay down specific arsenic limits for fish, shellfish and other seafoods, and we

recommend that the exemptions covering them should be maintained. We have however noted the recommendation of the COT that the relative toxicities of the marine organo-arsenicals should be assessed; and we are also aware that research is being conducted into the absorption and excretion by man of arsenic from fish. We wish to be informed in due course of the results of this work so that we may have the opportunity of reconsidering the need for arsenic limits in this area in the light of any new information.

18. We do however *recommend* that sea cucumber and similar sea food not currently exempted should be considered in the same way as fish and other marine products for the purposes of the Regulations in relation to the presence of naturally occurring arsenic in view of a report from a public analyst that the arsenic content of a sample of sea cucumber had been found to exceed the general limit of 1 ppm.

Beverages, ready to drink

19. The present Regulations specify arsenic limits of 0.1 ppm for non-alcoholic beverages, 0.2 ppm for alcoholic beverages and 0.5 ppm for black beer and mixtures of black beer and rum. The available evidence indicates general compliance with the present limits, whilst changes in manufacturing practices suggest that there is no longer any need for different limits within this group. We *recommend* therefore that the new limit for all beverages, ready to drink, should be 0.1 mg/kg.

Beverages, concentrated

20. The present Regulations specify a limit of 0.5 ppm for soft drinks for consumption after dilution. This allows for the fact that dilution of such products reduces the concentration of arsenic present to approximately the levels found in those beverages for which a limit of 0.1 ppm is currently specified. In the case of retail sale the limit of 0.5 ppm applies to all concentrates regardless of dilution ratio but in the case of sale to a manufacturer of soft drinks this limit only applies to concentrates having a dilution ratio no greater than 10:1. Super-concentrated soft drinks with a dilution ratio of 40:1 are now on the market and when sold to a manufacturer these would at present be exempt from the 0.5 ppm limit (although the general limit of 1.0 ppm would still be applicable). The available evidence indicates general compliance with the 0.5 ppm limit where it is applicable and we therefore *recommend* that this limit be retained and extended to cover all concentrated soft drinks irrespective of intended dilution ratio or intended use.

Arsenical feed additives

21. Our attention has been drawn to the fact that organic arsenical compounds are sometimes added to the feeds of pigs and poultry for veterinary purposes. The main compounds used are sodium arsanilate and roxarsone (monosodium-3-nitro-4-hydroxy-phenylarsonate). Sodium arsanilate is used at levels up to 100 mg/kg in pig feed as a growth promoter and at levels up to 400 mg/kg to control swine dysentry. The recommended withdrawal period is 10 days. Roxarsone is used as a growth promoter for pigs at levels up to 38 mg/kg feed and for poultry at levels up to 50 mg/kg feed. In this case the recommended withdrawal period is 7 days. If these withdrawal periods are observed, the levels of arsenic in offal should be less than 1 ppm, the general limit laid down in the current Regulations, and in muscle tissue much less than this.

22. Arsenical compounds used in on-the-farm medication were the subject of Recommendations made in 1968 under the Veterinary Products Safety Precautions Scheme. Notes covering the protection of consumers for 3-nitro-4-hydroxy-phenylarsonic acid stated that provided 4-hydroxy-3-nitrophenylarsonic acid is added to feed for pigs at the recommended rate of 25 to 37.5 ppm and is withdrawn from the feed for a period of not less than 10 days before slaughter its use should not lead to residues (expressed as ppm of elemental arsenic) in excess of 0.3 ppm in liver and 0.2 ppm in meat and should not be a hazard to consumers. Although the dose rate now used remains the same as in 1968, the recommended withdrawal period has changed from 10 days to 7 days. The results of a recent monitoring programme of pigs' kidneys which we have seen have shown only one sample out of 65 exceeding 0.15 mg/kg. However, it has come to our attention that, even when the recommended dosages and withdrawal periods have not been observed, pig kidney may still comply with the Arsenic in Food Regulations. In the light of this evidence, therefore, we have concluded that the maximum arsenic content of pig kidney and pig liver should not exceed 0.5 mg/kg if medicinal additives are used as recommended; and in order to ensure that recommended withdrawal periods are observed we consider that this limit should be included in any new Regulations. However, we also consider that in the interests of consistency this limit should be applied to all animal and poultry tissues (though not to fish). We *recommend* accordingly.

Chemicals for which a limit is not specified in other regulations

23. The limits contained in the existing Regulations do not apply to any food in respect of which the maximum permitted arsenic content is prescribed by any regulations, other than the Arsenic Regulations themselves or amendments to them, made under the Food and Drugs Act 1955 or by any order having effect as if contained in Regulations so made. Otherwise the

existing Regulations specify a limit for 'Chemicals not otherwise specified' of 2 ppm.

24. The limit specified on the arsenic content of food additives in other UK legislation made under the Food and Drugs Act 1955, and in various international specifications including those from the EEC, is generally 'not more than 3 mg/kg'. In the interests of simplicity and consistency we consider that the Arsenic in Food Regulations should also specify a limit of 3.0 mg/kg for chemicals for which a limit is not specified in other regulations, and we *recommend* accordingly.

Iron powder intended for use in the preparation of flour

25. The present Regulations specify a limit of 10 ppm for iron powder intended for use in the preparation of flour. This limit was introduced in 1972 through the Bread and Flour (Amendment) Regulations 1972[a] and relates to the use of iron powder as one of the forms of iron in which that nutrient may be added to flour under the terms of the Bread and Flour Regulations 1963[b], which require that all flour must contain not less than 1.65 milligrams of iron per 100 grams of flour. The figure of 10 ppm was adopted following representations from the trade that it was not always possible to comply with the previous limit of 5 ppm for, 'reduced iron intended for use in the preparation of flour'. It was accepted at the time that the change from 5 ppm to 10 ppm was most unlikely to result in a measurable increase in the arsenic content of flour, and we *recommend* that a limit of 10.0 mg/kg should be retained for the time being; the revocation of this special provision should however be considered in relation to the proposed revocation of the requirement to add iron as a nutrient to flour, as contained in the proposals for new Regulations governing the composition and labelling of bread and flour which were issued in April 1983.

Summary of Recommendations

26. We *recommend* that:

(a) the regulations should be maintained, though they should also be amended and simplified at a suitable opportunity (paragraph 10) as set out below;

(b) proportions of arsenic should be expressed as milligrams per kilogram (mg/kg) in future Regulations (paragraph 11);

(c) the maximum permitted arsenic level for food, other than specified food, should be maintained at 1.0 mg/kg (paragraph 12);

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[a] SI 1972 No. 1391

[b] SI 1963 No. 1435

(d) in the definition of 'substantial quantity', the percentage should be reduced from 25% to 10%, and provision should be made for the case of additive premixes not for retail sale (paragraphs 13 and 14);

(e) the exemptions for fish and edible seaweed, and products made from them, contained in Regulation 3(2)(b)[(a)] should be maintained and extended to all sea food, but it is proposed to review the situation when more information is available on the relative toxicities of the marine organo-arsenicals (paragraphs 17 and 18);

(f) the only foods for which there should be specified limits differing from the general limit in future Regulations should be as set out at (g) to (l) below (paragraph 15);

(g) 'beverages, ready to drink' should be subject to a statutory limit of 0.1 mg/kg (paragraph 19);

(h) 'beverages, concentrated' should be subject to a statutory limit of 0.5 mg/kg, irrespective of intended dilution ratio or intended use (paragraph 20);

(j) 'animal and poultry tissues' should be subject to a statutory limit of 0.5 mg/kg (paragraph 22);

(k) 'chemicals for which a limit is not specified in other regulations' should be subject to a statutory limit of 3.0 mg/kg (paragraph 24);

(l) 'iron powder intended for use in the preparation of flour' should continue for the time being to be subject to a statutory limit of 10.0 mg/kg; though the revocation of this special provision should be considered in relation to the proposals for new Regulations governing the composition and labelling of bread and flour as issued in April 1983 (paragraph 25).

FAC/REP/39 **1983**

(a) SI 1959 No. 831

APPENDIX I

List of those who made representations or gave information

Association of Public Analysts
Association of Sea and Air Port Health Authorities
Barrow-in-Furness Borough Council
Bedfordshire County Council
Berkshire County Council
Beverley Borough Council
Birmingham, City of
Brewers' Society
Cadbury Schweppes Ltd
Cleveland County Council
Cornwall County Council
Croydon, London Borough of
Cumbria County Council
Durham County Council
Dyfed County Council
Food Manufacturers' Federation
Gloucestershire County Council
H J Heinz Company Ltd
Humberside County Council
Kent County Council
Lancashire County Council
Leicestershire County Council
Merseyside County Council
Mid-Glamorgan County Council
Moir and Palgrave, Public Analysts
Monksland District Council
National Association of Cider Makers
National Federation of Consumer Groups
Norfolk County Council
Northumberland County Council
Nottinghamshire County Council
Port of London Health Authority
Shropshire County Council
Somerset County Council
Staffordshire County Council
Vale of Glamorgan Borough Council
West Midlands County Council

APPENDIX II

COMMITTEE ON THE TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

REPORT ON THE REVIEW OF THE ARSENIC IN FOOD REGULATIONS

Terms of Reference

To advise at the request of:

Ministry of Agriculture, Fisheries and Food
Department of the Environment
Department of Health and Social Security
Department of Trade
Health and Safety Executive
Medicines Commission, Section 4 Committees and the Licensing Authority
Committee on Medical Aspects of Food Policy
Home Office
Scottish Home and Health Department
Department of Agriculture and Fisheries for Scotland
Welsh Office
Department of Health and Social Services, Northern Ireland
Other Government Departments

1. To assess and advise on the toxic risk to man of substances which are:

   (a) used or proposed to be used as food additives, or used in such a way that they might contaminate food through their use or natural occurrence in agriculture, including horticulture and veterinary practice, or in the distribution, storage, preparation, processing or packaging of food;

   (b) used or proposed to be used or manufactured or produced in industry, agriculture, food storage or any other workplace;

   (c) used or proposed to be used as household goods or toilet goods and preparations;

   (d) used or proposed to be used as drugs, when advice is requested by the Medicines Commission, Section 4 Committees or the Licensing Authority;

   (e) used or proposed to be used or disposed of in such a way as to result in pollution of the environment.

2. To advise on important general principles or new scientific discoveries in connection with toxic risks, to co-ordinate with other bodies concerned with the assessment of toxic risks, and to present recommendations for toxicity testing.

Membership

The following have served on the Committee during the preparation of this Report:

Professor P Turner, MD, BSc, FRCP, Hon MPS, Hon FI Biol *(Chairman)*
Professor F Beck, DSc, MD, ChB, LRCP, MRCS
Professor A E Bender, PhD, FRSH, FIFST
Professor B E Clayton, MD, PhD, FRCP, FRC Path
Professor D S Davies, PhD
J McL Philip, Esq, MRCVS, FI Biol
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Professor O Wrong, DM, FRCP, FRCPE

Joint Secretaries

Professor F A Fairweather, QHP, MB, BS, FRC Path, FI Biol
B H MacGibbon, BA, BM, BCh, MRC Path
Mrs S J Hattersley, BSc
W H B Denner, Esq, PhD
M A Garley, Esq

Assessors

T J Coomes, Esq, BSc, FIFST
M J Griffiths, Esq

Representatives of the following Government Departments assisted the Committee with the preparation of this Report:

Department of Health and Social Security
Laboratory of the Government Chemist
Ministry of Agriculture, Fisheries and Food
Scottish Home and Health Department

Introduction

1. We were requested by the Food Additives and Contaminants Committee (FACC) to consider the Report on the Survey of Arsenic in Food compiled by the Working Party on the Monitoring of Foodstuffs for Heavy Metals and in the context of the FACC Review of the Arsenic in Food Regulations to assess hazards to health that could arise from arsenic in food and to review present information on the toxicity of arsenic. A review of the pharmacokinetics and toxicology of arsenic precedes consideration of possible health hazards from the quantities of arsenic in the United Kingdom diet. Our conclusions and recommendations are presented in the final section.

Absorption of Arsenic

2. The extensive range of arsenicals has not been comprehensively studied for absorption in man or animals although a number of individual compounds have been investigated to varying degrees. Three routes of absorption have been established, the gastro-intestinal tract, the lung and the skin(1,2)[a]. Water solubility and the physical form of inorganic arsenicals appear to have generally a greater influence on absorption than the chemical characteristics of individual compounds(1). Soluble trivalent and pentavalent inorganic compounds such as sodium arsenite ($NaAsO_2$) and sodium arsenate (NA_2HAsO_4) are well absorbed and presumptive evidence indicates that less soluble compounds like lead arsenate ($PbHAsO_4$) are comparatively poorly absorbed (3,4).

3. In animal studies, composition of the concomitant diet may also affect gastro-intestinal absorption of inorganic arsenicals with casein and hydrolysed casein reducing the amounts absorbed. Arsenic binding to these food substrates was not evident(5). The implication of these findings, which were derived from the experimental use of arsenic trioxide (As_20_3), for the human environment require elucidation.

4. The overall situation for organo-arsenicals is not well defined. Excluding those compounds which are naturally present in marine foods it is considered that the trivalent organo-arsenicals are generally poorly absorbed while the pentavalent forms are absorbed in varying amounts(6) with some, for example the herbicide cacodylic acid (dimethyl arsinic acid), showing significant absorption(7). Organo-arsenicals which are present in fish and shellfish appear to be of relatively high molecular weight (*c*400); arsenobetaine ($Me_3AsCH_2CO_2$) has been identified as one of these compounds(8). Evidence suggests that the marine food organo-arsenicals may be readily absorbed from the gastro-intestinal tract(9,10).

Distribution of Arsenic

5. The total human body content of arsenic has been estimated at between 3 and 4 mg and tends to increase with age(11). Arsenic is widely distributed in the body including liver, kidney, lung, spleen and skin, with the highest concentration in the hair and nails. Other organs have been shown to accumulate arsenic for example muscle, uterus, bone and neural tissue. Only total arsenic can be measured with accuracy in tissues as the available techniques

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[a] Numbers in brackets refer to the table of References at the end of this Report.

change the original valence state of the arsenic during the digestion of the tissues(12). Differences in distribution between trivalent and pentavalent arsenic have not been elucidated in man.

6. Human studies with radio-labelled inorganic arsenic (Arsenic 74) administered intravenously as trivalent arsenite(13) and orally as the pentavalent compound arsenic acid(14) indicate a three compartment distribution. It appears that arsenic rapidly equilibrates in the extracellular space and there is subsequent distribution into a second and third compartment. Organ identification of these compartments is speculative but may include kidney, liver and muscle. Both studies reflect a small residual pool of arsenic held in a third compartment with a half life of about 10 days to 40 days, perhaps longer. Placental transfer of arsenic can occur with deposition in fetal tissues(15,16).

Indices of arsenic exposure

7. Blood and tissue levels of arsenic are unreliable indices of arsenic exposure due to the wide variation in blood arsenic values in non-excessively exposed people, the lack of a generally accepted critical organ and the fact that only total arsenic, but not the valence state, can be accurately measured in human biological tissues(17). Urinary arsenic has a normal wide variation but average values for exposed workers have been shown to be significantly raised. The concentration of arsenic in hair and nails may be useful in confirming arsenic intoxication if the sampling strictly avoids external contamination.

Biotransformation and Excretion of Arsenic

8. In humans there is evidence for ingested arsenic in the form of inorganic trivalent and pentavalent compounds undergoing methylation prior to excretion in the urine along with unchanged inorganic arsenic(10,18). The methylated compounds so far identified all contain arsenic in the pentavalent form and could account for a substantial proportion of the original compounds ingested. Peak excretory level for the unchanged (minor) inorganic component precedes that for the (major) methylated compounds. Faecal excretion of arsenic from ingested inorganic compounds which are well absorbed accounts for only a small percentage of the administered quantity(14).

9. The fate of organic arsenicals has not been clearly defined in man. It may be reasonably assumed that methylated compounds like cacodylic acid are fairly quickly excreted unchanged in the urine(19). Limited information on the organo-arsenicals present in fish and shellfish indicates that these compounds appear to be readily excreted in the urine in an unchanged chemical form with most of the excretion occurring within two days of ingestion(9,10).

Arsenic Toxicity

10. It is common practice to express arsenic exposure in terms of elemental arsenic (As) but this masks the pharmacokinetic and toxicological differences of the range of arsenic compounds present in the environment. Arsenic is rarely present in the free state in the environment but is widely distributed as both inorganic and organic compounds. The arsenic radical exists in the oxidation states As^{-3}; As^{+3}; As^{+5}; with As^{o} as the elemental form. Inorganic and organic trivalent (As III) and pentavalent (As V) compounds exist as either naturally formed substances or as synthesised and industrially prepared chemicals such as the organo-arsenical pesticides.

11. The toxicological potentials of the arsenicals broadly conform to a pattern of trivalent forms being more toxic than pentavalent forms and inorganic compounds more toxic than organic compounds, but there are exceptions to this generalisation and factors such as solubility, particle size, rate of absorption, metabolism and excretion may have a significant influence on toxicity. Using information from a variety of sources, human and animal observations, groups of arsenical compounds have been ranked in decreasing order of toxicity(20): arsines (trivalent inorganic or organic); arsenite (inorganic); arsenoxides (trivalent with two bonds joined to oxygen); arsenate (inorganic); pentavalent arsenicals such as arsonic acids; arsonium compounds (four organic groups with a positive charge on arsenic); metallic arsenic.

12. Many of the toxicological effects of arsenic especially the trivalent form, are believed to be associated with its reaction with cellular sulphydryl (–SH) groups(21,22,23). Thus tissues rich in oxidative systems are often affected, particularly the gastrointestinal tract, kidney, liver, lung and epidermis. The overall effect produced by the consequent inhibition of enzyme systems essential to cellular metabolism is the depression of fat and carbohydrate metabolism and also cellular respiration. Pentavalent arsenic is capable of uncoupling mitochondrial oxidative phosphorylation. This effect may be due to a competitive substitution of arsenate for inorganic phosphate and the formation of an unstable arsenate ester which is quickly hydrolysed. The significance of this action of pentavalent arsenic is unclear but it may relate to the neurological manifestations of arsenic toxicity(24).

13. For many years interest in the toxicological effects of arsenical substances has had an emotive content and there is opinion that on occasions arsenic has been wrongly identified as the cause of episodes of poisoning and its aetiological significance in some diseases inadequately proven(25). However, there is no doubt that arsenical compounds can be toxic with morbidity and sometimes mortality in animals and man. Descriptions of the clinical manifestations of arsenic poisoning are available in standard texts and a brief outline only will be given.

14. In acute or sub-acute arsenic poisoning the clinical signs in decreasing order of frequency include fever, diarrhoea, emaciation, anorexia, vomiting, increased irritability, exanthemata and hair loss(24). The presenting signs in chronic toxicity are often dermatological (melanosis, keratosis, desquamation, finger nail changes), haematological (anaemia, leucopenia) or hepatic enlargement(24). Arsenicals have a number of systemic effects(6) and those aspects related to chronic exposure are of particular interest.

15. The effect of inorganic arsenic on the circulatory system appears to be dose related with mild vasodilatation in response to small doses and larger doses producing generalised capillary dilatation with increased permeability. The response is pronounced in the splanchnic area especially on exposure to the trivalent inorganic compounds. Renal involvement is often apparent in acute or sub-acute arsenic poisoning but usually only the more severe cases of chronic arsenic exposure show overt kidney effects. Varying degrees of renal tubular necrosis and degeneration result in toxic arsenic nephrosis.

16. Dermatological effects of chronic ingestion of low doses of inorganic arsenicals show initially as cutaneous vasodilatation then later as hyperpigmentation and hyperkeratosis with subsequent atrophy and degeneration of the skin. Limited evidence suggests that after a period of time malignant tumours may develop. The neurological system may be affected by chronic exposure to inorganic arsenic compounds with the development of peripheral neuritis and in severe cases there is involvement of the spinal cord. A substantial number of patients surviving severe acute inorganic arsenic poisoning later develop a variety of neurological problems. It is thought that organic arsenicals rarely affect the nervous system (6).

17. Blood and bone marrow are affected by inorganic arsenicals with anaemia and leucopenia. It is possible that an inhibition of folic acid metabolism may account for some of the haematological effects of arsenic toxicity(26). In addition, disturbance of mitochondrial haem biosynthesis by inorganic arsenate results in porphyrinuria(27). Although organo-arsenicals seem rarely to affect the haemopoietic system agranulocytosis has been reported(6). The liver is particularly susceptible to the toxic effects of inorganic arsenicals. There is fatty infiltration, central necrosis and cirrhosis. The hepatic parenchyma is usually involved but there may also be pericholangitis, with total effects ranging from mild disturbances to acute yellow atrophy and death.

Mutagenicity of Arsenic

18. Sodium and potassium arsenite, sodium arsenate, arsenic trichloride and a number of organo-arsenicals have been assessed for mutagenic properties in a variety of studies. Chromosomal aberrations have been detected in both mammalian and non-mammalian cells exposed in vitro to inorganic (including sodium arsenite and arsenate) and organic arsenicals. The effects of arsenicals as a group in the Rec-assay (Bacillus subtilis) and Reversion-assay (Escherichia coli, Salmonella typhimurium) have been variable although

sodium arsenite (the only compound to be tested in both screens) gave positive results(28).

19. Studies on lymphocytes from workers(29) and patients(30,31) either currently or previously exposed to arsenic showed an increased frequency of chromosomal aberrations over comparable controls. A similar study(32) revealed a significantly higher frequency of sister chromatid exchange, but no increase in chromosomal aberrations. In vitro exposure of normal human lymphocytes to sodium arsenate has produced a dose-dependent increase of sister chromatid exchange and chromosomal aberrations(33).

20. The mechanism by which chromosomes are affected by arsenicals is unclear. Inhibition of DNA repair has been proposed(34) and more fundamentally the inhibition of phosphorus incorporation into nucleic acid(30). The mutagenic potential of arsenicals is somewhat difficult to reconcile with the negative outcome of animal carcinogenicity studies(35) but would support the tumour data accumulated in man.

Teratogenicity of Arsenic

21. Sodium and potassium arsenate and sodium arsenite have been investigated in animal studies for arsenic induced teratogenic effects. These and other arsenicals have been administered as single doses at specific times of gestation via the intravenous, intraperitoneal or oral routes and also by feeding or dermal application throughout most of the pregnancy(36,37,38). A variety of animals have been studied including mice, rats, hamsters, rabbits and sheep. It appears that parenterally administered single doses of sodium arsenite of about 10 mg/kg body weight in mice produce significant fetal abnormalities compared with 20–40 mg/kg or greater for sodium arsenate in mice, rats and hamsters. Oral dosages over the short term require to be about three times greater than the corresponding parenteral dosages to produce fetal effects. The long term feeding of four pregnant ewes throughout most of the pregnancy with 0.5 mg/kg potassium arsenate had no effect(36,37).

22. Recognising the species variation in susceptibility to teratogenic effects of chemical substances the significance of these animal studies, and the relevance of the amounts of arsenicals administered, to the human situation with average environmental exposure remains undetermined. Nevertheless the occurrence of fetal abnormalities in animals exposed to inorganic arsenicals, albeit at relatively high dosages and in artificial circumstances, is to be noted. Survey information from an ore smelting plant in Sweden which emitted arsenic, lead, mercury, cadmium and sulphur dioxide into the environment showed an increase in fetal abnormalities in children born to female workers who continued employment at the smelter during pregnancy(39). No data is available which implicates arsenic independently as a human teratogen.

Carcinogenicity of Arsenic

23. The carcinogenicity of arsenic has been investigated in a variety of animal studies with inorganic arsenic (arsenic trioxide; sodium arsenite; sodium arsenate and lead arsenate) administered via a number of routes including dermal application, oral administration, intratracheal instillation and sub-cutaneous injection(40). These studies have produced essentially negative results and contrast with the apparent relationship between arsenic over-exposure and cancer emerging from epidemiological observations and case histories(41-52). Epidemiological studies in areas with a raised arsenic content in drinking water have shown a higher cancer mortality than in comparable non-arsenical areas, with respiratory and alimentary cancer accounting for nearly threequarters of the cancer deaths(41,42) and a relatively high incidence of skin cancer which increased with increases in the arsenic content of the water and age of the individual(43,44).

24. The aetiological links between arsenic exposure and tumour formation have been the subject of much debate and the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment when considering this issue in 1979 concluded 'Arsenic trioxide should be considered as an established human carcinogen'.

Chronic Arsenic Exposure and Effects

25. Inorganic arsenic has been assessed to have a long biological half-life, depending on body distribution(13,14) and therefore has the potential to accumulate from the daily amounts absorbed from environmental exposure. In circumstances where continued daily intakes of arsenic exceed the total daily elimination progressive accumulation is likely to occur. The normal content of arsenic in the human body has been estimated at between 3 and 4 mg(11) and by inference these total tissue deposits of arsenic may be tolerated by man without untoward effects. However prolonged exposure to increased amounts of arsenic can produce chronic toxic effects and there appears to be an increased prevalence of a number of diseases including malignant tumours (see paragraphs 23 and 24 above). The clinical conditions observed in populations which ingest raised amounts of arsenic over prolonged periods are illustrated by studies in regions with elevated levels in water: Cordoba (Argentina)(41,42), Antofagasta (Chile)(52,53,54) and a defined area on the west coast of Taiwan(43,44).

26. In the Cordoba region it was found that palmo-plantar hyperkeratosis was the commonest manifestation shown by the inhabitants and about 12% of epitheliomas diagnosed at a local regional dermatological clinic were in patients showing signs of chronic arsenicism. The mortality in this region due to cancer was higher than in comparable non-arsenical areas, with respiratory and alimentary cancers accounting for nearly threequarters of the deaths.

27. Assessment of clinical conditions presenting in 180 Antofagasta inhabitants revealed an increased prevalence of hyperkeratosis, chronic cough, Raynaud's syndrome and chronic diarrhoea in patients exhibiting abnormal skin pigmentation. Infants and children with chronic arsenic poisoning showed much greater severity of symptoms than adult and senile patients. Almost 20% of children with chronic arsenical dermatosis had Raynaud's phenomenon. Autopsy examination of four children with chronic arsenicism demonstrated fibrous thickening of small and medium sized arteries with significant luminal obliteration.

28. A general survey of about 40% of the population of the defined area in Taiwan identified overall prevalence rates (per thousand) for skin cancer (10.6), keratosis (71.0) and hyperpigmentation (183.5). All three conditions tended to increase with age. Blackfoot disease (a local term for a peripheral vascular disorder resembling thromboangiitis obliterans) which results in gangrene of the extremities, especially the feet, had an overall prevalence of 8.9 per thousand. This prevalence increased with duration of exposure and arsenic content of the water.

Arsenic concentration in water and chronic toxic effects

29. Identification of the arsenic chemical species and content in the water of areas with endemic arsenicism would assist in the assessment of tolerable arsenic intakes by ingestion via food and drinking water. Comprehensive data are not available but the information derived from a number of studies is of some value.

30. In Cordoba samples at separate sites showed sodium arsenite levels up to 4.5 mg/1 (2.6 mg/1 arsenic), sodium arsenate at 1.6 mg/1 (0.64 mg/1 arsenic) and arsenic trioxide at 2.8 mg/1 (2.1 mg/1 arsenic). The chemical species of the arsenic in Antofagasta is not known but the arsenic concentrations ranged from 0.05 to 0.96 mg/1 with a geometric mean of 0.598 mg/1 for the period 1955–1970. In Taiwan the arsenic content of the well-water ranged from 0.01 to 1.82 mg/1 with many of the wells having an arsenic content of around 0.4 to 0.6 mg/1. The chemical form of the arsenic is unknown. In Nova Scotia(55) the medical findings associated with a survey of well-water for arsenic revealed that out of 33 people using water with arsenic concentrations >0.1 mg/1, 23 (70%) had mild symptoms and signs possibly attributable to arsenic poisoning whereas only 25 out of 86 people (29%) consuming water with arsenic at >0.05mg/1 were similarly affected.

31. An overall consideration of the quantities of arsenic in the water of these various areas allows the tentative conclusion that overt chronic arsenicism can be associated with water supplies with an upper level of arsenic contamination of around 1 mg/1 or greater, and concentrations of 0.1 mg/1 may give rise to presumptive symptoms of toxicity. Allowing a daily water intake of 1.5 litres it appears that arsenic intakes of about 1.5 mg per day are likely to result in chronic arsenic toxicity and daily amounts of 0.15 mg may also be toxic in the long term to a proportion of the population. The chemical species of arsenic contributing to these intakes were not determined but it would not be unreasonable to consider them in terms of inorganic arsenic.

ARSENIC IN FOOD

Exposure to Arsenic

32. Arsenic is absorbed by ingestion, inhalation and also via the skin. Ingested arsenic is the main source of intake for the general public with food providing the major amount and water usually significantly less. The average intake from water appears to be less than 50 µg/week and even in a region supplied with water from an area with raised soil arsenic content most intakes are likely to be less than 100 µg/week. Furthermore part of this difference arises from differences in the limits of detection of the methods of analysis used (5 µg/litre and 10 µg/litre respectively). In general air contributes only minor amounts to the total arsenic intake, assessed to be about 1 µg/week. Dermal absorption is probably only of significance in occupational or accidental contact exposures and from the use of topical arsenical medicaments.

33. Arsenic intake can be increased by raised amounts in food and water, occupational exposure which may involve inhalation or dermal absorption, and also to a declining extent by the systemic or topical use of arsenic containing medicaments. Contamination of tobacco by arsenical pesticides during cultivation has been recognised in the past(56) and the smoking of such tobacco would contribute to arsenic intake by inhalation.

Dietary Arsenic

Monitoring surveys

34. Information accumulated by the Working Party on the Monitoring of Foodstuffs for Heavy Metals from the surveys carried out by the Ministry of Agriculture, Fisheries and Food (MAFF), the Laboratory of the Government Chemist (LGC) and the Department of Agriculture and Fisheries for Scotland (DAFS) allows an assessment of the current dietary intake of arsenic in the general population of the United Kingdom. These surveys comprised measurement of the average daily intake of arsenic using the revised methodology of the Total Diet Study(57) and the arsenic content of individual foods, including all the staple foods, fish and shell-fish and many minor dietary food components.

35. The Committee on Toxicity considers that similar surveys need only be conducted periodically for the provision of data from which updated assessment of dietary arsenic intake can be made and reviewed. Additional information will be required for definitive assessment of the dietary arsenic intake of special groups such as children, pregnant women and individuals consuming unusual diets. The contamination of foods obtained from abnormal or changing horticultural environments should also be monitored.

Dietary arsenic intake

36. In the United Kingdom food is normally the major source of arsenic intake and is estimated to provide on average 89µg of arsenic per day (0.62 mg per week) with a daily range of about 50–150µg (0.35–1.05 mg per week). The fish group of foods contributes up to three-quarters of the dietary arsenic. Estimates from food surveys in other countries are useful for broad comparison but differences in patterns of food consumption and assessment of dietary intake make direct comparisons inappropriate. Thus estimates from North America(58) indicating lower intakes in 1971–4 (about 15µg/day) than in the United Kingdom should be viewed in this context.

37. The suggested FAO/WHO maximum acceptable daily load of arsenic from all sources is 50µg per kilogram body weight(59), which corresponds to a daily intake of 3.5mg for a 70 kilogram adult. Total arsenic intakes in the United Kingdom from food, water and air are well below the maximum amounts suggested by the FAO/WHO with average *weekly* UK values of 0.40–1.15mg (the upper figure includes the highest amounts estimated for food and water). It is considered that the quantities of arsenic ingested from average diets by the general public in the United Kingdom give no cause for concern.

Marine food organo-arsenicals

38. The consideration of body intakes of arsenic purely in terms of the elemental substance may neglect toxicological differences between the constituent arsenic compounds. Organo-arsenicals from marine foods provide a high proportion of the dietary arsenic and there is no indication that they present a toxicological hazard. As there is little information on these compounds and their toxicological potential comprehensive chemical identification and toxicological assessment of members of this group of arsenicals is therefore desirable. If the marine organo-arsenicals prove not to have significant toxicological properties there may be a case for considering fish and shellfish arsenic separately from that obtained from other food sources. In general, quantitative data on the chemical species of arsenic in foods and beverages would be advantageous.

Maximum Permitted Arsenic Levels in Food

39. In the United Kingdom virtually all of the food sampled contained *substantially less* arsenic than the concentrations permitted under the Regulations(60,61,62) and this is reflected in the assessed average dietary intake from the food survey data. The arsenic levels achieved within the existing Regulations indicate that there is no toxicological basis at the present time for a further reduction in permitted levels in food or beverages. Periodic monitoring of the major dietary items for arsenic content and also the form of arsenic present is considered desirable and identified increases of arsenic in specific foods should be reviewed in the context of the total dietary intake.

CONCLUSIONS AND RECOMMENDATIONS

40. Our *conclusions* are as follows:

(a) The average dietary intake of arsenic in the United Kingdom gives no cause for concern and there is no toxicological indication to lower the permitted limits for arsenic in food. Total arsenic intakes from food, water and air are well below the maximum acceptable daily load of arsenic of 50µg/kg body weight (3.5 mg for a 70 kg adult) suggested by the FAO/WHO, with average *weekly* United Kingdom values of 0.40–1.15 mg.

(b) The toxicity of arsenic compounds is influenced generally by the chemical species of arsenic and modified by physical factors. Ideally arsenic intakes should be specified in qualitative as well as quantitative terms. The amounts of arsenic in some fish (especially shellfish) are considerably higher than for most foods and this is reflected in the fact that about threequarters of the average dietary intake of arsenic consists of marine organo-arsenicals. Little toxicological data is available on these compounds but there is no evidence to suggest that arsenic in fish presents a hazard to human health.

(c) There is insufficient data to provide exact threshold levels for arsenic exposure leading to chronic toxic effects. However we consider that daily ingestion of about 1.5 mg of inorganic arsenic is likely to result in signs of chronic arsenic toxicity and intakes of about 0.15 mg per day may result in arsenicism in some individuals. These amounts of arsenic are within the FAO/WHO suggested maximum acceptable daily load of 50µg/kg body weight (3.5 mg for a 70 kg adult) but it must be recognised that the FAO/WHO figure was derived from *normal* dietary intakes of arsenic by persons not exposed to special occupational hazards. Thus the maximum suggested daily load provides a figure for a total arsenic intake from all the chemical forms present in a normal diet, and is not applicable to an intake composed largely of inorganic arsenic.

(d) There is epidemiological evidence of an association between the exposure of humans to inorganic arsenic and increased cancer risk but no carcinogenic effect has been demonstrated in animals. The mechanisms involved in the cases in man are not known but it seems unlikely that a genotoxic mechanism is involved. Exposure to levels of arsenic below the toxic range do not appear to carry a carcinogenic risk.

41. Accordingly, we *recommend:*

(a) that monitoring surveys on the arsenic content of food should continue, but need only be conducted periodically for an assessment of average dietary arsenic intake. If possible these surveys should include assessment of the dietary arsenic intake of special groups such as children and individuals consuming unusual diets;

(b) that in general quantitative data on the chemical species of arsenic in food and beverages would be advantageous;

(c) that food obtained from abnormal or changing environments should be monitored for arsenic contamination;

(d) and that the relative toxicities of the marine organo-arsenicals should be assessed.

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